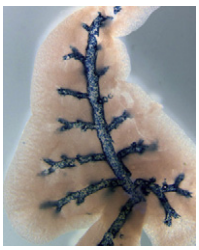
Cell Stem Cell

Editors' Notes

Airing Issues on Epithelial Progenitors

Although epithelial layers are on the surface relatively simple histological structures, both the lung and the skin—and indeed any other lined organ—include a multitude of cell types and regionally varied architecture that add significant complexity to the tissues as a whole. Precise identification of individual cells that are responsible for epithelial regeneration in either location, during homeostasis and/or in response to injury, is challenging. In this issue Hogan and coauthors use a lineage-tracing assay to demonstrate that Clara cells of the lung epithelium serve as a stem cell population in some regions of the airway but do not give rise to alveolar epithelial cells. In his Preview of the Hogan paper, Alan Fine discusses the current findings and highlights some of the remaining questions in the lung stem cell field. In contrast to the lung, the lineage potentials of subpopulations of skin epithelium have been extensively studied both in vivo and in vitro. In the first of a trio of stem cell niche minireviews presented in this issue, Elaine Fuchs describes one of the stem cell populations in the skin, the basal layer of the interfollicular epidermis. Her analysis includes a discussion of some of the intrinsic and extrinsic signals that regulate the stem cell population in this niche and mediate their transition into the spinous, suprabasal epithelial layer.

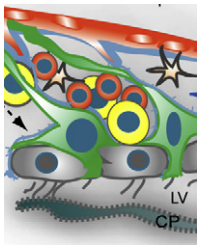


Back and Forth in the Blood

Hematopoietic stem cells have been known for many years to reside in the adult bone marrow, but their precise location and the regulatory components of their niche remain the subjects of debate. In their minireview, Garrett and Emerson discuss recent evidence that supports a model for a complex and situational niche for HSCs. In particular, the authors suggest that HSCs likely inhabit perivascular regions in the steady state but may be more dependent on stromal and endosteal support during periods of regeneration. The role of specific signaling cascades, including Wnt and Notch, in HSC regulation has also been the subject of some controversy. In this issue, two independent reports from the Gilliland and Aifantis laboratories report that conditional disruption of the Hedgehog (Hh) signaling cascade does not lead to measurable defects in adult hematopoietic function, contrasting with the conclusions of at least some previous studies. Clearly, despite being often touted as the ''best-understood'' mammalian stem cell population, the HSC field still faces a string of fundamental questions that remain to be settled.

The NSC World Is … Flat?

The growing support for the model that HSCs exist in a perivascular niche parallels relatively recent findings that indicate that neural stem cells also contact endothelial cells in vivo. Indeed, as described by Miller and Gauthier-Fisher in the third minireview in our series, NSC niches that contact blood vessels have been characterized for multiple neurogenic locations in the brain. Determining the architecture and cellular composition of these regions may point to novel NSC regulatory inputs that could be harnessed to expand functional populations in vitro and in vivo, as well as offering insights as to how to avoid inappropriate growth or differentiation of oncogenic populations. Another advance that may provide a valuable tool for the latter goal is described by Dirks and colleagues in their Resource article. By modifying specific culture conditions used to grow NSCs, the authors developed an efficient method to propagate glioma cell lines that recapitulate aspects of human disease. Notably, this method results in adherent cultures as opposed to the more conventional sphere-forming conditions, opening the door for high-throughput screening and perhaps in the future even patient-specific isolates that could be tested with specific interventions.



Manipulating Pluripotency

Determining the developmental origin and in vivo regulation of pluripotency is a long-standing question, and several articles in this issue address it in varying ways. In one of a pair of Perspective articles, Nichols and Smith outline their views regarding the initiation of pluripotency in the embryo, how these lessons may be applied in vitro to isolate and interconvert ESCs and EpiSCs from different species, and what these findings might teach the field about manipulating artificially generated pluripotent cells. In the second Perspective, Hayashi and Surani approach the question by considering the origin of germ cells and discuss how embryonic differentiation events regulate epigenetic modifications that specify pluripotency during development. In addition, the authors raise the question as to whether reprogrammed somatic cells have truly regained complete pluripotent status without passing through the germ cell state. Pluripotent cells do appear to exist in a range of discrete states, with a certain propensity for transitioning from one to another (see *4*: 387, *3*: 480), although the functional relationships between them remain unclear. Also in this issue, Jaenisch and colleagues report that by conscripting the transcription factor pathways that participate in reprogramming to form iPSCs, pluripotent populations can be derived from NOD mice, which until this point have been believed to be refractory to this process. Their results underscore several of the points raised in the two Perspective articles and highlight the fact that culture conditions can indeed shift cells from one pluripotent state to another.